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Pathological Ventricular Remodeling: Mechanisms: Part 1 of 2

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Abstract

Despite declines in heart failure morbidity and mortality with current therapies, re-hospitalization rates remain distressingly high, impacting substantially on individuals, society, and the economy. As a result, the need for new therapeutic advances and novel medical devices is urgent. Disease-related left ventricular remodeling is a complex process involving cardiac myocyte growth and death, vascular rarefaction, fibrosis, inflammation, and electrophysiological remodeling. As these events are highly inter-related, targeting one single molecule or process may not be sufficient. Here, we review molecular and cellular mechanisms governing pathological ventricular remodeling.

Keywords

remodeling; cell death; apoptosis; autophagy; hypertrophy; fibrosis; inflammation; electrophysiological remodeling; stem cells; progenitor cells

Introduction

It is predicted that as our population ages, the direct medical costs of all cardiovascular diseases (including hypertension, coronary heart disease, stroke, and heart failure) will triple, reaching $818 billion in 2030[1]. Prominent within this population of patients are the five million Americans who suffer from chronic heart failure, the final common pathway of many forms of heart disease and the most common discharge diagnosis in Medicare for several years running. This syndrome carries a mortality of approximately 50% at 5 years, and its incidence and prevalence are expanding rapidly around the globe. Thus, not only is the problem of heart failure enormous and growing, it contributes importantly to runaway medical costs just as society is moving swiftly to contain those costs. As a result of these converging influences, we are at a crucial juncture where novel therapeutic approaches for heart failure are sorely needed. To accomplish this, comprehensive understanding of biological processes leading to heart disease and disease-related ventricular remodeling is required.

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In the setting of disease, the left ventricle (LV) manifests a robust plasticity response which has been termed pathological remodeling[2, 3]. This process is the culmination of a complex series of transcriptional, signaling, structural, electrophysiological, and functional events occurring within the cardiac myocyte. In addition, other cellular elements within the ventricle participate, including fibroblasts (promoting fibrosis), vascular smooth muscle cells (promoting vascular stiffness), vascular endothelial cells (promoting endothelial dysfunction), and leukocytes (promoting inflammation) (Figure). Current thinking holds that these events – the heart's response to a variety of pathological insults – confer short-term benefit. However, left unchecked, these remodeling events are maladaptive and predispose to cardiovascular morbidity and mortality.

Current therapies, including angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), aldosterone antagonists, and β-adrenergic receptor blockers (β-blockers), manifest significant efficacy in reducing morbidity and mortality in patients with chronic systolic heart failure[4]. However, in many instances disease progression continues unabated. Further, less is known about the substantial proportion of disease where systolic performance of the LV is preserved. Also, whereas novel disease targets are continually being discovered, most therapeutics do not demonstrate consistent efficacy in patients; indeed, many prove to be ineffective, even deleterious, before reaching Phase III clinical trials. Here, we review many of the major molecular and cellular pathways governing LV remodeling in the two broad types of heart failure, that with reduced (HFrEF) or preserved (HFpEF) systolic function. In an accompanying article, we review relevant therapies[5].

Classification of heart failure

Most current therapies, and clinical trials to evaluate novel therapies, target HFrEF, previously termed systolic heart failure. However, it is estimated that 50% of heart failure patients have a preserved left ventricular ejection fraction, or HFpEF[6]. Initial studies attributed HFpEF to dysfunction of the myocardium during the filling phase of the cardiac cycle; diastolic stiffness, prolonged isovolumic LV relaxation, and slow LV filling were attributed to pathological dysfunction of the ventricular myocyte during diastole[7]. However, it is clear that in some instances, the left ventricular myocardium is an innocent bystander, manifesting dysfunctional filling due to volume overload, insufficiency of perfusion, or inadequate filling times[8]. In many instances, it is likely that a combination of perturbed diastolic relaxation[9] and excessive volume due to extrinsic factors[8] combine to perturb ventricular filling.

Vascular stiffening and generalized systemic vascular dysfunction are observed in patients with HFpEF[10, 11]. Reduced aortic distensibility and increased end-systolic elastance lead to exaggerated fluctuations in blood pressure for the same change in afterload and preload[6]. Indeed, therapeutic strategies that specifically target ventricular-arterial stiffening improve exercise tolerance in elderly, hypertensive individuals[12]. In addition, impaired flow-mediated vasodilation has been observed, implicating endothelial dysfunction in HFpEF pathophysiology and suggesting the possibility of benefit with therapies targeting nitric oxide bioavailability[13]. Pulmonary hypertension is also associated with HFpEF, and elevated pulmonary artery pressures predict mortality in HFpEF patients[14].

Whether HFrEF and HFpEF are truly distinct disorders, or rather represent a syndrome that exists across a spectrum, is unknown. Also, within each of the two broad categories of HFrEF and HFpEF, a wide variety of disease etiologies dictate pathogenesis. In other words, heart failure, a syndrome defined on clinical terms, derives from numerous different diseases, such as myocardial infarction, hypertension, cytokine or neuroendocrine dyscrasias, genetic disorders, and more. One prominent example where “personalized

medicine" has emerged to parse these elements is hypertrophic cardiomyopathy (HCM), where distinct genetic variants have been identified and which are informative in predicting phenotype and outcome[15]. Classically, familial HCM is caused by mutations in sarcomeric genes that control cardiac myocyte myofilament movement and calcium handling. At least one-third of patients presenting with HFpEF have normal extracellular matrix proteins (e.g. collagen) suggesting that cardiomyocyte stiffness due to sarcomeric aberrations also contributes to pathogenesis. It is conceivable that genetic testing for familial HCM may aid in accurately diagnosing HFpEF early on.

Familial dilated cardiomyopathy (DCM) can manifest mendelian patterns of inheritance, and mutations in at least 50 genes have been identified and linked to familial DCM[16]. These include sarcomeric genes, including those coding for proteins localized to the Z disk, nuclear membrane proteins, and proteins involved with connections to the plasma membrane. As with HCM, not all patients with DCM manifest the same phenotype. Importantly, some genetic variants, even within families, can cause either HCM or DCM, which renders diagnosis and risk prediction difficult based on genetic testing. Recently, however, mutations in the gene coding for the giant, sarcomeric protein, titin *(TTN)* have been identified in 25% of patients with familial idiopathic DCM, whereas only 3 of 231 patients with HCM harbor these mutations[17]. Mutations in this gene can also promote cardiomyocyte stiffness[18] which can contribute to HFpEF. Therefore, testing for mutations in *TTN* may aid in differentiation of disease etiology and early diagnosis.

As research continues, more genetic mutations and polymorphisms will be identified, such as race-driven genetic predispositions[19] that lead to cardiomyocyte stiffness or fibrosis. However, predicting disease based on genotype is further complicated by the fact that modifying genes, epigenetic factors, and environmental influences contribute to the complexity of the disparate phenotypes.

HFpEF is observed commonly in older women with a history of hypertension. Difficulty treating HFpEF derives, at least in part, from its segregation with multiple co-morbidities and a lack of standard definition[20]. In fact, trials using ACE inhibitors[21], ARBs[22], and β-blockers[23] have failed to demonstrate efficacy in patients with HFpEF. Aldosterone antagonists are currently being tested in an NIH-funded trial called TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with Aldosterone Antagonist) (clinicaltrials.gov, NCT00094302).

Although current therapies have decreased overall morbidity and mortality in patients with HFrEF, individual responses are not uniform. For example, some heart failure patients on ACE inhibitor therapy harbor increased plasma Ang II levels, suggesting that ACE inhibition is incomplete[24]. Patients also respond variably to mineralocorticoid receptor antagonists (MRAs)[25, 26]. Inhibition of β-adrenergic signaling is standard-of-care for HFrEF patients[27]. However, beta-adrenergic receptor polymorphisms can render antagonist treatment ineffective[28]. New therapies targeting beta-receptor downstream effectors are being developed[29].

Hypertensive ventricular remodeling

High blood pressure is the single most important risk factor for heart failure; approximately 75% of heart failure cases have antecedent hypertension[30]. As terminally differentiated cardiac myocytes are inefficient at reentering the cell cycle, these cells respond to pressure-overload stress by enlarging. This response, termed hypertrophy, ultimately leads to ventricular wall thickening and stiffening.

Based on Laplace's law, ventricular wall stress is proportional to both ventricular pressure and cavity radius and inversely proportional to wall thickness[31]. Thus, increases in wall thickness tend to diminish wall stress, decrease oxygen demand, and hence are adaptive. When the pressure stress is persistent, however, the myocardium slowly transitions to a state of decompensation and clinical heart failure. Our understanding of mechanisms underlying this transition from adaptive hypertrophy to maladaptive failure remains incomplete.

In recent years, a large number of preclinical studies have demonstrated that blunting load-induced hypertrophic growth of the LV is possible, even in the presence of persistent afterload stress, without compromising contractile performance[32-34]. These studies, then, have uncovered a potentially new target of anti-remodeling therapy, the hypertrophic phenotype itself. This strategy is based on the notion that while short-term hypertrophic remodeling may be adaptive, serving to normalize wall stress and oxygen demand, persistent, long-term activation of this response is detrimental. If true, suppressing pathological hypertrophy may be key to impeding progression to heart failure[32]. Suggestive evidence in humans supports therapeutic targeting of the hypertrophic process[35].

Atrophic remodeling

One goal of antihypertensive therapy is to slow, arrest, or possibly even reverse the progression of cardiomyocyte growth. Indeed, the cardiac myocyte is capable of significant shrinkage or atrophy[36]. This shrinkage leads to reductions in LV mass and occurs under conditions of mechanical unloading (prolonged bedrest, mechanical support with a left ventricular assist device, weightlessness during space travel) or increased catabolic state (e.g. cancer)[37-39]. Atrophy is an energy-consuming process that involves changes in both anabolic and catabolic processes[40].

Whether atrophy is associated with changes in cardiac function may depend on its magnitude, duration, and inciting factors. In a small number of patients with cachexia, significant loss of LV mass was not associated with specific cardiac abnormalities as compared with non-cachectic patients[41]. However, short-term mechanical unloading in animals by heterotopic heart transplantation can reverse hypertrophy, whereas long-term unloading was associated with decreased function and increased fibrosis[42]. Current investigations are ongoing to determine whether cardiac atrophy causes diastolic dysfunction during long-duration space flight[37].

Ventricular remodeling in ischemic heart disease

Coronary artery disease is a leading cause of HFrEF[43]. In fact, most of our knowledge regarding LV remodeling is derived from patients and animal models of myocardial infarction. The extent of myocardial damage, as well as its location within the LV, directly impacts the magnitude of LV remodeling[44]. Underlying mechanisms derive directly from the infarction itself, including cell death and loss of contractile activity in the affected zone, as well as secondary ventricular dilation and remodeling in infarct-remote zones due to enhanced hemodynamic burden[43]. Over time, a process termed “infarct expansion” occurs, wherein unremitting mechanical forces stretch the abnormally stressed tissue. The end-result is a dilated LV with abnormal levels of wall stress and distorted and ineffective contractile performance.

Reperfusion of the occluded, infarct-related artery is key to minimizing infarct size and maintaining ventricular performance[45]. Significant advances in our understanding of the biology of ischemic heart disease, including the critical importance of restoration (percutaneous angioplasty) and maintenance (drug-eluting stents, anti-thrombotic agents) of arterial perfusion to the at-risk zone have culminated in robust improvements in clinical

outcomes[45]. Although these advances have provided significant declines in mortality, the LV will inexorably, over subsequent months and years, remodel in response to abnormally elevated load and demand, leading to ventricular dilation and ultimately dysfunction[43].

Remodeling of the LV following myocardial infarction has been divided into stages[44]. Following interruption of arterial perfusion from occlusion of a coronary vessel, death of cardiac myocytes immediately ensues. These cells die via necrosis, apoptosis, or possibly autophagy. Although cardiac stem cells have been identified in the adult heart, and cardiac myocytes themselves are capable of re-entering the cell cycle under only limited circumstances[46-48], myocyte proliferation does not contribute significantly to the response to infarct-related wave of cell death. In the next stage of infarct healing, dying cardiac myocytes release intracellular proteins into the circulation and trigger an inflammatory response. Inflammatory cells, including neutrophils, monocytes, macrophages, and lymphocytes, infiltrate the tissue. These immune cells remove dead myocytes and pave the way for healing. After the resolution of the inflammatory response, cardiac fibroblasts proliferate and secrete extracellular matrix proteins, such as collagen I, to form a fibrotic scar that replaces dead myocytes. The resulting tightly cross-linked, fibrotic scar with significant tensile strength serves to prevent rupture. This remodeling of the LV continues progressively in response to increases in wall stress, provoking cardiac myocyte hypertrophy in the infarct border zone, wall thinning, and chamber dilation. This global adverse remodeling response leads to increases in both LV end-diastolic and end-systolic volumes and reduced ejection fraction[43].

Contributing cellular events

Cardiac Myocyte Death

Biology—Cardiac myocytes carry out the contractile function of the myocardium, and they are largely incapable of replication; hence, their survival is crucial. Following myocardial injury, cardiac myocytes undergoing necrosis lyse, releasing intracellular contents, some of which can be detected in the blood and used as markers of injury (e.g. creatine kinase, cardiac troponins). Apoptosis, an energy-dependent, programmed cell death response, does not entail release of intracellular contents and does not trigger an inflammatory response; it is reversible up to a “point of no return”. An emerging literature suggests that necrosis may itself be a programmed cellular process, rather than uncontrolled disintegration of the cell[49]. Further, recent evidence suggests that necrosis and apoptosis are integrally linked and may be different faces of a single process (“necroptosis”)[49].

Often, dying cells manifest evidence of up-regulated autophagy, an evolutionarily ancient process of ordered recycling of intracellular contents[50, 51]. Considerable debate has centered around whether this autophagic cascade reflects the cellular response to stress, serving to promote cell survival, or represents a process which, itself, contributes to cell death[52]. Consensus has emerged recently, however, that at least in some instances, autophagic cell death (programmed cell death type II) exists[53], including in heart muscle[54]. That said, divergent views exist[52]. Irrespective of whether autophagy can trigger cardiomyocyte death, considerable evidence supports a model where cardiomyocyte autophagy can be adaptive or maladaptive, depending on the context[55-59].

As a Therapeutic Target—Although all three types of cell death/intracellular remodeling occur within the heart, it is not entirely clear whether these are truly distinct and discrete events or represent a continuum of overlapping biochemical and molecular processes. Nevertheless, selective inhibitors targeting apoptosis (caspase inhibitors), necrosis (inhibitors of mitochondrial permeability transition pore [MPTP] opening), and necroptosis (necrostatin 1) have been employed in the heart[60]. Suppression of apoptosis decreases

adverse remodeling and subsequent progression to heart failure in models of ischemia/reperfusion[61], MI-induced heart failure[62], and nonischemic cardiomyopathy[63]. However, optimal timing of therapy, targets for inhibition within apoptotic signaling cascades, precise mechanisms of inhibition, and even the cell types involved, remain unresolved. Of note, several pharmacological therapies in current clinical use may suppress cell death. For example, Ang II and norepinephrine can each trigger cardiomyocyte apoptosis, and their respective blockers antagonize these responses[64, 65].

Cardiac Myocyte Hypertrophic Growth

Biology

A central tenet in cardiac biology is the notion that most adult cardiac myocytes are terminally differentiated cells and therefore do not proliferate; rather, they respond to stress by growing, shrinking, or dying. Recent work has revealed that a fraction of cells within the ventricle are, in fact, capable of re-entering the cell cycle and proliferating[46-48, 66, 67], although the size of this fraction is the subject of intense debate. Nevertheless, the preponderance of evidence indicates that the majority of cardiomyocytes are incapable of dividing and respond to stress by eliciting a hypertrophic growth response. As part of this, a wide range of transcriptional and post-translational events occurs, including activation of a pattern of gene expression reminiscent of that observed during fetal development ("fetal gene program").

Besides mechanical loading, cardiac myocytes respond to a variety of other growth cues, including cytokines, growth factors, catecholamines, vasoactive peptides, and hormones. Some evidence suggests that cell size is regulated by shared signaling pathways, whereas cell shape and sarcomeric organization are regulated by distinct pathways[68]. If borne out by additional studies, this observation might facilitate precise definitions of cellular phenotype-specific regulatory mechanisms.

As a Therapeutic Target

Although no therapeutic agents target hypertrophic growth directly, some strategies in current use alter the hypertrophic response secondarily, including suppression of neurohormones (catecholamines, Ang II, aldosterone), calcium (e.g. L-type Ca^{2+} channel blockers), or preload (e.g. vasodilators or diuretics). However, efficacy of these strategies varies and is dependent on the pathway that is modulated. Further, as there is redundancy among these pathways, downstream points of convergence may be more suitable to inhibit or reverse cardiac hypertrophy. Potential targets include oxidative stress, serine/threonine phosphatases, non-gated Ca^{2+} influx/Ca^{2+} signaling, downstream effectors of rapamycin or G-protein-coupled receptors, protein kinases, and chromatin remodeling agents (e.g. histone deacetylases)[69].

Overlapping mechanisms exist in pathological (pressure overload) and physiological (exercise) hypertrophic growth, such as increased expression of genes responsible for cardiac myocyte structure, ion transport, and proteolysis[70]. However, genes associated with metabolic processes and muscle contraction may be up-regulated to a greater extent in response to exercise[70]. Furthermore, capillary growth does not keep pace with myocyte growth in disease models, which, in concert with fibrotic change, limits oxygen delivery to the myocardium[71, 72].

Cardiac Myocyte Hyperplasia

Biology

Whereas growth of the adult heart has been classically held not to involve a significant hyperplastic response, recent evidence has demonstrated existence of progenitor cells resident within the myocardium, as well as cardiomyocytes capable of re-entering the cell cycle, findings which contradict the traditional idea that the heart is a strictly post-mitotic organ[46-48, 66, 67]. These dividing cells may participate in cardiac homeostasis at basal levels and potentially replace dying cardiac myocytes, albeit, at low levels. Cardiac progenitors include cells characterized by expression of cell surface markers including c-Kit[73], Sca-1[74], or Islet-1[75], and cardiac "side population" (SP) cells[76]. Self-adherent clusters of cells termed "cardiospheres" have been developed from human biopsy specimens[77, 78]. The neonatal heart harbours cardiomyocytes capable of re-entering the cell cycle, promoting wound repair[47, 79].

Cardiac progenitors have been localized to the epicardial surface of the heart, where they contribute to coronary vasculature formation during embryogenesis[80]. These epicardial cells are pluripotent and migrate into the myocardium, undergoing epithelial-to-mesenchymal transition to give rise to multiple cell types[81, 82]. Nevertheless, cardiac stem cells, regardless of their true identity, are unable to mount a proliferative response sufficient to replace dying myocardium in the setting of injury. One goal is to develop pharmacological strategies that enhance regenerative potential of resident progenitor cells sufficient to contribute to reversal of tissue loss[83].

Fibrosis

Biology

A hallmark feature of ventricular remodeling is deposition of excessive extracellular matrix (ECM). This surplus ECM, which constitutes "scar" or fibrosis, promotes both contractile dysfunction and rhythm disturbances[84]. As a result, cardiac fibrosis contributes to morbidity and mortality in many forms of heart disease. Indeed, the amount of fibrotic scar in the myocardium correlates strongly with increased incidence of arrhythmias and sudden cardiac death[85-87].

ECM deposition and fibrosis formation occur through the action of cardiac fibroblasts. In the setting of pathological stress, fibroblasts proliferate and differentiate into myofibroblasts, thereby gaining the capacity to contract and secrete collagen I, collagen III, and fibronectin[84]. Proliferation and activation of these cells, the most abundant cell type in the myocardium, derives from a variety of sources, including resident fibroblasts, adult epicardial cells undergoing endothelial to mesenchymal transition[81, 88], and circulating, collagen-secreting bone marrow-derived cells[89].

Scar formation following myocardial infarction arises from replacement fibrosis, where regions of myocyte "drop out" are replaced by scar. In contrast, fibrosis arising during hypertension-induced pressure overload and in remote regions following myocardial infarction is reactive (perivascular or interstitial), leading to decreased compliance and diminished oxygen diffusion capacity. Both individual myofibroblasts and collagenous septa within the left ventricle facilitate and propagate the arrhythmic phenotype of the remodeled heart[90, 91].

As a Therapeutic Target

Cardiac fibrosis is an independent and predictive risk factor for heart failure in both ischemic and non-ischemic cardiomyopathy[92-94]. Recent work has demonstrated that cardiac

fibrosis, long held to be irreversible, may regress under certain circumstances[81, 95]. Some evidence suggests that modulation of cardiac fibrosis alters the arrhythmic phenotype in patients with heart disease[96, 97]. To date, no therapeutic strategy has been developed to specifically target fibrosis in the heart. Cardiac fibroblasts are unique and phenotypically distinct from fibroblasts isolated from other tissues (as reviewed elsewhere[98]); they also display phenotypic heterogeneity within the heart itself. In addition, the precise phenotypes of fibroblasts from normal, injured, and failing hearts are ill defined, and mechanisms underlying the transition from normal wound healing to maladaptive fibrotic remodeling remain unresolved. Interestingly, the abundance of newly formed, thin collagen fibers increases in the remote region of infarcted heart, but decreases with time in the infarct zone, suggesting collagen maturation in the infarct zone[99]. Furthermore, neurohormonal inhibition leads to an increase in scar maturation while diminishing remote, reactive fibrosis[100]. As infarct-associated scar is necessary to prevent ventricular rupture, it may be advantageous to target new collagen fiber formation to allow for scar maturation.

Irrespective of these challenges, there is reason to believe that therapies focusing on cardiac fibrosis may prove salutary in the treatment of ventricular remodeling. Some therapies in current use may target, at least in part, cardiac fibroblasts. Specifically, Ang II provokes cardiac fibroblast proliferation and net accumulation of collagen *in vitro* and cardiac fibrosis *in vivo*[101, 102]. Interestingly, expression of Ang II receptors in cardiac fibroblasts exceeds that in cardiac myocytes[103], and ARBs appear to have antifibrotic actions[104]. In patients with hypertensive heart disease, losartan reduced cardiac fibrosis and serum collagen markers[105]. In addition, treatment with HMG Co-A reductase inhibitors (“statins”) resulted in reduced fibrosis and reduced collagen synthesis[106, 107]. Small molecule inhibitors of histone deacetylases (HDACs) attenuate fibrosis in a preclinical model of pressure overload[108] via mechanisms involving transcriptional silencing of the gene coding for connective tissue growth factor (unpublished observations).

Inflammation

The immune system plays a significant role in ventricular remodeling, and its persistent activation may lead to long-term cardiac injury. Specifically, activation of a variety of inflammatory molecules and pathways, the complement system, T cells, and the formation of autoantibodies have been reported in heart failure patients[109-111]. Consequently, a number of strategies have been proposed to mitigate the harm caused by these inflammatory events; most have failed[112, 113]. In the 1970's, it became apparent that immunosuppression with glucocorticoids or nonsteroidal anti-inflammatory agents conferred risk in patients with ischemic heart disease[114, 115]. More recently, however, early results of studies seeking to decrease autoantibody titers are promising[116]. High doses of intravenous immunoglobulin therapy to neutralize autoantibodies and the complement system improve heart failure symptoms, but long-term use is required[117, 118]. The few trials using immunoadsorption therapy in patients with dilated cardiomyopathy, where autoantibodies are thought to play a role in pathogenesis, were promising[119, 120]. Therapeutic plasma exchange, where large amounts of plasma are removed from the circulation and replaced with 5% albumin, potassium chloride, calcium gluconate, and then terminally supplemented with immunoglobulins to replace the removed proteins, is being tested[121].

Vascular Remodeling

Biology

A wide range of cardiovascular diseases are marked by vascular remodeling. For example, both hypertension and immunosuppressive treatment are associated with vessel wall thickening[122, 123]. In preclinical models of myocardial infarction, hypertrophy in the border

zone of the infarct is associated with diminished coronary flow reserve, increases in the media/lumen ratio, and increases in medial thickness[124].

Development of significant coronary collateral circulation is a major mechanism of vascular remodeling. A recent meta-analysis reported diminished mortality risk in patients with high collateralization compared to those with low collateralization[125]. Another study reported that while collaterals may be protective during early stages of infarct healing, after infarction is complete their presence is not an independent predictor of clinical outcome[126]. Some evidence suggests that promoting angiogenesis in the setting of pressure overload can protect the heart from injury[127].

As a Therapeutic Target

A large number of clinical trials of therapeutic neovascularisation employing gene or protein therapies have failed. This failure may stem, at least in part, from single, high dose administration of therapy[128]. For example, short-term exposure to VEGF (vascular endothelial growth factor) leads to leaky vessels that regress, whereas prolonged exposure promotes formation of more stable vessels[129]. To address this, novel polymers that degrade slowly and sustain release of growth factors have been employed[130]. However, it is unlikely that a single growth factor will be sufficient to promote neovascularization and limit adverse remodeling. Therefore, development of proangiogenic therapies will likely require combination therapy comprising multiple growth factors, such as FGF-2, HGF, MCP-1, GM-CSF, PDGF-BB, TGF-β[131]. In addition, careful selection of end points in trial design and appropriate methods for evaluating those end points may increase the likelihood of success of future proangiogenic therapies. Mode of delivery as well as timing of delivery may also be important.

As some of these growth factors tend to promote salvage of ischemic myocardium, early treatment may prove beneficial. Conversely, a study employing a mouse model of cardiac-specific induction and inactivation of a VEGF-sequestering soluble receptor reported that VEGF activity even at late stages of heart remodelling was sufficient to rescue function[132]. This study also suggested that a point-of-no-return may still exist, as augmenting neovascularization at late time points did not reverse fibrosis or myocyte hypertrophy.

Metabolic remodelling

Biology

Patients with diabetes and obesity are at increased risk of developing coronary artery disease, hypertension, and heart failure[133]. Under normal physiological conditions, the metabolic demands of the heart are met by metabolism of fatty acids and glucose, and to a lesser extent lactate and ketone bodies[134]. With the onset of insulin resistance and obesity-driven type II diabetes, uptake of metabolic substrates into cardiomyocytes becomes dysfunctional; fatty acid utilization is increased at the expense of glucose, which contributes to myopathy characterized by ventricular dilation, cardiomyocyte hypertrophy and death, interstitial fibrosis, and perturbations of diastolic relaxation. In animal models of obesity, triglycerides accumulate in the heart coupled with impaired mitochondrial function to oxidize the increased lipid load[135]. Several molecular and cellular mechanisms have been implicated in diabetic cardiomyopathy, including disordered activation of forkhead transcription factors, mTOR (mammalian target of rapamycin), microRNAs, mitochondrial dysfunction, the unfolded protein response, proteasome activation, and autophagy[136, 137].

The term “obesity paradox” has been coined to describe the association between obesity and improvements in heart failure outcomes[138]; among patients with similar heart failure severity, obese patients manifest improved survival compared with normal-weight

patients[139], and higher BMIs are associated with lower mortality risk[140]. Whether this association relates to mechanism is unknown, but conceivably may be attributed to depression of the neurohumoral system or an increase in nutritional or metabolic reserve. For example, the adipokine, leptin, which regulates appetite and energy balance has direct cardioprotective effects against ischemia/reperfusion injury[141].

The obesity paradox was tested in animal model, where insulin-insensitive rats were fed a high-fat diet and compared to insulin-insensitive lean rats, allowing for measurement of an effect of obesity in isolation. Obese rats manifested relative ischemia/reperfusion tolerance associated with activation of RISK (reperfusion injury salvage kinase) and nitric oxide synthase signalling pathways[142].

The myocardium itself can have direct effects on metabolism within other organs. For example, natriuretic peptides such as ANF (atrial natriuretic factor) and BNP (B-type natriuretic peptide) are secreted from cardiomyocytes in response to stress[143]. These peptides, circulating levels of which are elevated in heart failure, have lipolytic effects on adipose tissue, which is specific to primates[144]. Recently, it was reported that cardiomyocyte-specific expression of MED13, a transcriptional regulator, or pharmacologic inhibition of miR-208a, antagonizes high-fat diet-induced obesity and improves insulin sensitivity and glucose tolerance[145].

As a Therapeutic Target

Therapy that specifically targets cardiomyopathy due to obesity and diabetes does not currently exist. However, some strategies targeting weight loss manifest benefit to the heart. Weight loss from lifestyle changes or bariatric surgery is associated with decreases in LV dimensions, wall thickness, mass, and left atrial dimensions[146]. Removal of subcutaneous fat by liposuction does not elicit beneficial metabolic changes[147]. Also, whereas orlistat (a gastrointestinal lipase inhibitor) and sibutramine (a monoamine reuptake inhibitor) both to lead to weight loss and glycemic homeostasis, they have no significant effects on cardiac structure or dimensions[148].

Recently, a proteasome inhibitor, MG-132, was shown to manifest anti-oxidative and anti-inflammatory functions in an animal model of diabetic cardiomyopathy[149]. In addition, inhibition of phosphodiesterase-5 with tadalafil attenuated inflammation, improved fasting glucose and triglyceride levels, decreased body weight and reduced infarct size in an ischemia/reperfusion injury model in obese, diabetic mice[150]. Synthetic mimetics of natriuretic peptides have been approved for treatment of acute heart failure, although the largest study so far of nesiritide, a recombinant form of human B-type natriuretic peptide, failed to detect improvements in mortality or rehospitalization[151].

Electrophysiological remodeling

Patients with left ventricular hypertrophy are at significantly increased risk of malignant arrhythmias, accounting for a substantial component of the mortality associated with cardiac hypertrophy. Indeed, arrhythmia, especially ventricular tachyarrhythmia, is a major cause of death in patients with left ventricular heart failure. Sustained ventricular tachycardia and/or ventricular fibrillation can occur immediately post-MI, during the remodelling process, or late following injury.

In recent years, “electrical remodeling”, a term which encompasses alterations in multiple electrogenic transport processes within the cardiac myocyte, has emerged as an important pathophysiological mechanism in many types of cardiac pathology[152, 153]. Yet, our understanding of mechanisms underlying the myriad facets of electrical remodeling is limited. As a result, means of treating hypertrophy-associated arrhythmias remain

disappointingly ineffective. Also, there is substantial evidence that alterations in transmembrane Ca^{2+} fluxes – a central feature of electrical remodeling – contribute to the pathogenesis of hypertrophy and failure by abnormally activating Ca^{2+}-responsive signaling pathways.

Mechanisms underlying ventricular arrhythmia are multifactorial, but they derive, at least in part, from disordered electrical currents arising from prolongation of ventricular action potentials[153]. The resulting delay in the recovery of excitability, a consistent feature of ventricular hypertrophy, predisposes to early and late after-depolarizations. Superimposition of myocardial fibrosis, with altered electrotonic coupling between cells, slowed conduction, and dispersion of refractoriness, exacerbates the pro-arrhythmic phenotype.

Lengthening of ventricular cardiomyocyte action potential duration is commonly observed in both cardiac hypertrophy and failure, a phenotype which contrasts with the action potential shortening in the stressed (fibrillating) atrium. In the setting of excessive afterload, action potential duration increases more in subepicardial myocytes than in subendocardial myocytes[154]. In a canine model of pacing-induced heart failure, action potential duration increased significantly more in mid-myocardial cells than in subepicardial cells[155].

Action potential prolongation is caused by a wide range of changes in myocyte ion channels and electrogenic ion transporters (reviewed elsewhere[153]). Briefly, loss of voltage-gated Na^+ channel inactivation leading to a late inward sodium current is increased in failing cardiomyocytes[156]. In addition, down-regulation of outward K^+ currents[157], up-regulation of inward Ca^{2+} currents, and changes in Ca^{2+} current inactivation all contribute[158, 159]. Indeed, in many models of heart failure, diminished outward, repolarizing current secondary to down-regulated K^+ channel levels (particularly I_{to}) is observed[152, 160].

In contrast with heart failure, up-regulated inward Ca^{2+} current contributes to action potential prolongation in ventricular hypertrophy, particularly in models of modest hypertrophy. In fact, the density of L-type Ca^{2+} current ($I_{Ca,L}$) may be inversely correlated with disease progression, being increased in mild-to-moderate hypertrophy and decreased in severe hypertrophy and failure. Importantly, entry of small amounts of Ca^{2+} from the extracellular space triggers release of much larger amounts of Ca^{2+} from intracellular stores, amplifying even modest changes in inward Ca^{2+} flux. Also, in many species, membrane impedance is relatively high during phase 2 of the action potential, so changes in $I_{Ca,L}$ have significant effects on action potential morphology and duration.

The Na^+-Ca^{2+} exchanger (NCX), which catalyzes the bidirectional exchange of three Na^+ ions for a single Ca^{2+} ion, is a major mechanism of Ca^{2+} elimination during diastole. As one net positive charge moves per reaction cycle, NCX generates a transmembrane current that approaches one-half the magnitude of $I_{Ca,L}$. Alterations in NCX activation in heart disease can contribute to late after-depolarizations and triggered ventricular activity.

Normal electrical conduction depends on cell-cell connections through gap junctions, such as connexin 43, and these connections can be disorganized in the failing heart disrupting normal impulse conduction[161]. Further, in the failing heart, phosphorylation of the ryanodine receptor by Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) results in calcium leakage from sarcoplasmic reticulum (SR)[162] with concurrent down-regulated expression of the sarco/endoplasmic reticulum Ca^{2+}-ATPase 2a (SERCA2a) and reduced Ca^{2+} uptake into the SR[163]. The resulting depletion of SR Ca^{2+} stores coupled with elevations in cytoplasmic Ca^{2+} potentiates development of ventricular arrhythmia[152].

Aging

Processes involved in maladaptive ventricular remodeling are age dependent, and most patients with heart disease are older. Indeed, one caveat to translating pre-clinical results into the human context is that most animal studies are performed using young animals. Mortality due to myocardial infarction increases with age, a fact not explained by larger infarcts[164]. Aging in mice is associated with an attenuated inflammatory response and decreased macrophage-mediated phagocytosis of dead cells[165]. In addition, aged mice have decreased numbers of myofibroblasts and perturbed extracellular matrix deposition resulting in malformed scar[165]. Cell death is also affected by age-related accumulation of mitochondrial damage and DNA mutations[166]. Cumulative organelle damage with age may also increase the need for clearance by autophagy, a process that declines with age[51]. Cardiomyocyte hypertrophy is more pronounced in aged heart, contributing to cardiac dysfunction[167], and the intrinsic capacity of the heart to regenerate diminishes with aging[46, 168].

Environmental Exposures

Cumulative environmental exposures alter disease risk, therapeutic responsiveness, biomarker expression, and cellular phenotypes in the heart. This can begin as early as during fetal development. Epidemiological data suggest that an adverse intrauterine environment increases the risk of cardiovascular disease in adulthood[169]. For example, prenatal hypoxia leads to altered expression of proteins such as protein kinase C epsilon, heat shock protein 70, and endothelial nitric oxide synthase[169]. However, these environmental exposures are not always mimicked reliably in preclinical studies using laboratory animals. Even when non-genetically modified laboratory rodents are fed a high fat diet to induce obesity and cardiac dysfunction, they do not develop atherosclerotic plaques as seen in humans. In chimpanzees, heart disease is primarily mediated by aberrant myocardial fibrosis and not vascular atherosclerotic plaque despite high levels of cholesterol and LDL[170].

Recently, sialic acid N-glycolylneuraminic acid (Neu5Gc), a molecule not synthesized in humans but found in red meat and milk products, was identified in the endothelium of human atherosclerotic plaque[171]. This sugar, foreign to humans but not other mammals, promotes generation of antibodies and inflammation and is associated with carcinoma progression in humans[172]. In a recent epidemiological study of major dietary sources, high red meat intake was associated with coronary heart disease[173]. These data raise the possibility that this sugar could be used as a biomarker for patient stratification and therapeutic effectiveness, as well as being a therapeutic target itself (e.g. generation of neutralizing antibodies). Recent evidence implicates intestinal microbiota in the link between red meat consumption and cardiovascular risk[174], as bacterial metabolism of red meat-derived l-carnitine can promote atherogenesis[175].

Sex Differences

Coronary artery disease, the leading cause of HFrEF, occurs more commonly in men than women[6, 176]. By contrast, HFpEF affects women more commonly than men by a proportion of 2:1. Underlying mechanisms remain unclear, although sex differences have been described in cardiac structure, left ventricular diastolic function, ventricular-arterial stiffness, and aging[177]. Males, both human and animal models, tend to develop eccentric LV remodeling in response to stress, whereas females develop concentric remodeling[177]. In addition, women display enhanced regression of LV hypertrophy after aortic valve replacement compared to men, suggesting enhanced susceptibility to afterload stress in women[178]. Cardiac structural differences have also been demonstrated in regards to concentric LV remodeling and systolic hypertension which are enhanced in aging women[179, 180]. This may be exacerbated by the co-morbidities of aging, such as obesity,

diabetes, and physical inactivity which may occur more frequently in women than men[181, 182].

One possible mechanism underlying sexual dimorphism in heart disease involves mutations in mitochondrial DNA. Mitochondrial DNA encodes proteins associated with oxidative phosphorylation and is inherited from the mother's egg. Therefore, mutations in mitochondrial DNA would be passed on only by women, which can lead to family cohorts in which the offspring of female members are at risk for disease, whereas the offspring of male members are not. Some mitochondrial DNA mutations or seemingly neutral mitochondrial DNA polymorphisms may not be pathogenic in offspring immediately, but rather lead to inability to adapt to aging or environmental exposures, triggering emergence of pathology later in life. In fact, mitochondria harboring mutant DNA may selectively proliferate in response to a defect in the respiratory electron transport chain, rendering these mutant mitochondria more prevalent in post-mitotic cells such as cardiac myocytes. Sex-specific hormones also affect mitochondria. Ubiquinol-cytochrome-c reductase, a component of complex III within the respiratory electron transport chain, is reduced in the absence of ovarian hormones[183].

Unlike the Y chromosome, the X chromosome is enriched in genes essential for development and viability. X-chromosome silencing occurs to inactivate one of the two X chromosomes in female cells. Originally, it was thought that silencing is maintained throughout the individual's lifespan; however, it has been shown more recently that loss of X-chromosome silencing can occur with aging[184]. Furthermore, approximately 15% of X-linked genes escape inactivation in a manner which differs across regions of the X chromosome[185]. Genomic imprinting of complex traits can also depend on sex[186].

Conclusion

Heart failure is exploding in incidence and prevalence around the world. Defined by clinical criteria, this syndrome derives from a wide range of underlying disease etiologies and is marked by a diverse spectrum of structural, functional, electrophysiological, cellular, and molecular events. At one level, it comes as little surprise that only a small number of therapeutic strategies have emerged with efficacy, given these complexities. The effects of genetic, neurohumoral, environmental, and age-related influences -- and more -- combine to dictate pathogenesis and clinical outcome. Ultimately, these complexities must be elucidated in the context of the individual patient to optimize therapeutic success. That the myocardium comprises a host of cell types, each manifesting unique transcriptional, signaling, remodeling, proliferative, and death responses, underscores the seemingly insurmountable complexity of the challenge we face. However, unequivocal successes achieved already, and the expanding scope of the problem, will continue to drive progress in this fascinating field.

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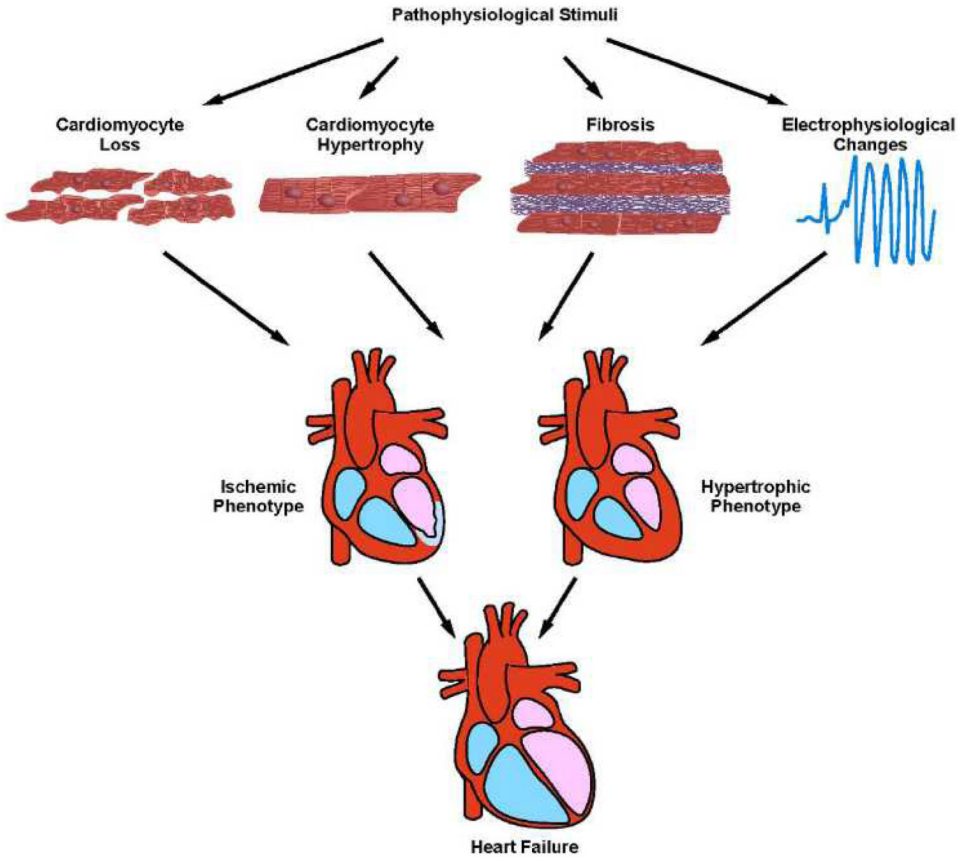

Figure.

Mechanisms of pathological ventricular remodeling. In response to pathophysiological stimuli, such as ischemia/reperfusion or excessive mechanical load, multiple molecular and cellular processes contribute to ventricular remodeling. These include cardiomyocyte loss through cell death pathways, such as necrosis, apoptosis, or possibly excessive autophagy. Cardiomyocytes become hypertrophic in response to both mechanical and neurohumoral triggers. Accumulation of excess extracellular matrix leads to fibrosis. Metabolic derangements, insulin resistance, and lipotoxicity can occur. Finally, structural changes and alterations in ion transporting processes culminate in a pro-arrhythmic phenotype.